Identifying Potential Kidney Donors Among Newborns Undergoing Circulatory Determination of Death

WHAT’S KNOWN ON THIS SUBJECT: The demand for donor kidneys for transplantation exceeds supply. En bloc kidney transplantation and donation after determination of circulatory death from pediatric donors increases the potential donor pool.

WHAT THIS STUDY ADDS: Newborn infants undergoing elective withdrawal of life support in the NICU are a previously unrecognized source of potential kidney donors.

abstract

BACKGROUND: Over 96,000 patients await kidney transplantation in the United States, and 35,000 more are wait-listed annually. The demand for donor kidneys far outweighs supply, resulting in significant waiting list morbidity and mortality. We sought to identify potential kidney donors among newborns because en bloc kidney transplantation donation after circulatory determination of death (DCDD) may broaden the donor pool.

METHODS: We reviewed discharges from our 84-bed NICU between November 2002 and October 2012 and identified all deaths. The mode of death among potential organ donors (weight ≥ 1.8 kg) was recorded. Patients undergoing withdrawal of life support were further evaluated for DCDD potential. After excluding patients with medical contraindications, those with warm ischemic time (WIT) less than 120 minutes were characterized as potential kidney donors.

RESULTS: There were 11,201 discharges. Of 609 deaths, 359 patients weighed ≥ 1.8 kg and 159 died after planned withdrawal of life support. The exact time of withdrawal could not be determined for 2 patients, and 100 had at least 1 exclusion criterion. Of the remaining patients, 42 to 57 infants were potential en bloc kidney donors depending on acceptance threshold for WIT. Applying a 40% to 70% consent rate range would yield 1.7 to 4 newborn DCDD donors per year.

CONCLUSIONS: A neonatal DCDD kidney program at our institution could provide 2 to 4 paired kidneys for en bloc transplantation each year. Implementing a DCDD kidney donation program in NICUs could add a new source of donors and increase the number of kidneys available for transplantation. Pediatrics 2014;133:e82–e87

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KEY WORDS
donation after circulatory determination of death, en bloc transplantation, kidney donation, kidney transplantation, newborns, NICU

ABBREVIATIONS
CPR—cardiopulmonary resuscitation
DCDD—donation after circulatory determination of death
ESRD—end-stage renal disease
OPO—organ procurement organization
WIT—warm ischemic time

Dr Hanley conceptualized and designed the study, supervised and participated in data collection, conducted the data analyses, and drafted the initial manuscript and subsequent revisions; Dr Kim and Ms Castleberry conceptualized and designed the study, participated in data collection, and critically reviewed the final manuscript; Dr Willey participated in data collection and critically reviewed the final manuscript; Dr Mathur conceptualized and designed the study, participated in data collection, assisted with the data analyses, and critically reviewed and revised the final manuscript; and all authors approved the final manuscript as submitted.

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According to the US Department of Health and Human Services National Kidney and Urologic Diseases Information Clearinghouse, >871,000 people were being treated for end-stage renal disease (ESRD) at the end of 2009. Between 1980 and 2009, the prevalence rate for ESRD in the United States increased nearly 600%, from 290 to 1738 cases per million. With advances in transplantation medicine and immunosuppression, kidney transplantation has become the treatment of choice for ESRD. Several studies have shown that kidney transplantation not only reduces waiting list morbidity and improves quality of life but also proves cost-effective compared with long-term dialysis.1–3 Due to these factors, the number of patients wait-listed for kidney transplantation has dramatically increased. According to the US Organ Procurement and Transplantation Network kidney transplantation database, there were 96,312 patients awaiting kidney transplantation as of May 2013, but only ~16,500 kidney transplants occur per year. In addition, each year ~35,000 patients are newly listed for kidney transplantation in the United States. Despite dialysis support, ~5000 patients die per year while on the waiting list.

The demand for donor kidneys has challenged transplant surgeons to seek innovative ways to increase the pool of potential kidney donors. One effective strategy is en bloc kidney transplantation, which allows the utilization of younger and smaller donors. This method involves transplantation of both kidneys from a single donor into 1 recipient. Previously, these smaller kidneys from younger donors were considered suboptimal for transplantation due to concern for increased graft thrombosis, hyperfiltration injury, and poor long-term graft survival. Recent studies, however, have shown that although en bloc transplants have increased the risk for graft thrombosis, they have low rates of hyperfiltration injury and actually have better long-term graft survival compared with size-matched recipients of single adult kidneys.4–6 Multiple studies have demonstrated that en bloc kidney transplants from pediatric donors to both adult and pediatric recipients have good clinical outcomes, including long-term graft survival and reduced rates of delayed graft function.7–11 Recent studies have shown good clinical outcomes with very small pediatric donors.6,12 Successful en bloc kidney transplantation from newborn and infant donors into both adult and pediatric recipients has recently been reported.13,14 In light of these cutting-edge surgical advances, our goal was to identify potential kidney donors among newborns undergoing elective withdrawal of life support in our NICU.

METHODS

The institutional review board at Loma Linda University approved this study. We conducted a review of the prospectively collected electronic database for our 84-bed level IIIC NICU that tracks admissions, discharges, and deaths. NICU discharges over a 10-year period from November 1, 2002, to October 31, 2012, were screened to identify all patients who weighed ≥1.8 kg at the time of death, which formed the primary inclusion criterion. The 1.8-kg weight cutoff was chosen because this is the smallest-size donor after determination of circulatory death (DCDD) that has successfully been used for en bloc transplantation (Richard V. Perez, MD, personal communication, May 2013). Medical records for all deceased patients who fulfilled the inclusion criteria were reviewed in detail to identify the mode of death. The mode of death was classified into 4 categories as previously described15,16: (1) brain death; (2) death with a do not resuscitate order in place; (3) death despite cardiopulmonary resuscitation (CPR); and (4) withdrawal of life support.

We examined the patients undergoing planned withdrawal of life support in greater detail. For these patients, we first recorded the underlying cause of death and significant comorbidities. To establish the eligibility for kidney DCDD, patients with medical contraindications to donation were excluded. These included HIV infection, systemic infection (positive blood or urine culture result within previous 72 hours or chronic infection), congenital renal abnormality, urine output <1 mL/kg per hour, or serum creatinine level ≥1.5 mg/dL. The interval between withdrawal and death was recorded for eligible patients to calculate warm ischemic time (WIT). We evaluated the number of potential donors based on time of death <60 minutes after withdrawal of life support; this WIT threshold is commonly used by US-based abdominal transplant surgeons to determine DCDD donor suitability. We also assessed donors with WIT from 60 to 120 minutes because the only center currently performing renal transplants with neonatal en bloc grafts (University of California Davis transplant program led by Dr. Richard Perez) uses a WIT threshold of up to 120 minutes. We further categorized these potential donors into 7 categories according to the underlying cause of death: neurologic, genetic/multiple congenital anomalies, inborn error of metabolism, complex congenital heart disease, respiratory failure due to lung pathology, prematurity, and congenital anomaly of the abdomen. The patients who fell into >1 category were categorized based on the cause that contributed the most to their death. We applied rates consistent with local and regional DCDD and donation after brain death consent rates to project the number of potential newborn kidney donors. Descriptive statistics
were used, and data are reported as median and range.

After we determined that there were no brain deaths in the NICU during the study period, we evaluated our 25-bed PICU donor data acquired from organ procurement organization (OPO) records to enable a comparison of organ-donor potential within our institution during the 10-year study period.

RESULTS

Study Cohort

From November 1, 2002, to October 31, 2012, there were 11,201 NICU discharges, of which there were 609 deaths. Three hundred fifty-nine infants weighed $\geq 1.8$ kg at the time of death. Of these, 145 (40.4%) patients died with a do not resuscitate order in place at the time of death, 55 (15.3%) died despite CPR, and 159 (44.3%) deaths occurred after elective withdrawal of life support. There were no brain deaths during this period.

Patients Undergoing Withdrawal of Life Support

The 159 NICU patients withdrawn from life support were 1 to 214 days old and weighed 1800 to 9845 g at the time of death. Among these, the exact time of withdrawal of life support could not be determined for 2 patients, and 100 had at least 1 exclusion criterion. Ventilator support was withdrawn in all 159 patients, and 57 patients also had inotropic support discontinued at the time of withdrawal. Seven patients had extracorporeal membrane oxygenation discontinued.

Suitable DCDD Donors

The WIT was 0 to 59 minutes in 42 patients and 60 to 120 minutes in 15 patients (Table 1). These potential donors had varied causes of death (Table 2). The majority (48% of patients with a WIT 0–59 minutes and 60% of patients with a WIT 60–120 minutes) died of an underlying neurologic cause or complex congenital heart disease. Of the 57 potential kidney donors, administration of comfort care medications was documented in 42 patients. These included continuous infusions of narcotics and/or benzodiazepines, intermittent dosages of narcotics and/or benzodiazepines, or a combination of both. No neuromuscular blockers were used. There was no record of additional comfort medications being given to 15 patients at the time of withdrawal.

Comparison With Local and Regional Organ Donation Activity

Based on OPO records, 143 patients were declared brain dead in our PICU during the 10-year study period, and 97 families (68%) consented to donation, resulting in 223 solid organ transplants. From January 2009 to June 2013, the DCDD consent rate was 52% at our hospital (donation authorization obtained for 16 of 31 potential pediatric and adult donors) and averaged 38% across 21 potential pediatric donors in 5 PICUs in the greater Los Angeles area.

DISCUSSION

A growing disparity between the waiting list for kidney transplantation and the number of available organs has led to the emergence of en bloc kidney transplants from infant donors as an innovative option that adds to the donor pool. Our data identified a previously unrecognized source of en bloc kidney donors: newborn infants undergoing elective withdrawal of life support in the NICU. Based on our data, 26% to 36% of neonates weighing $\geq 1.8$ kg could be potential DCDD kidney donors depending on the WIT cutoff that is used. The neonatal DCDD consent rate is yet unknown. The only study thus far that determined a PICU DCDD consent rate found it to be 53% at 1 center. We found a wide range of consent rates for donation activity in our region. These rates varied from 38% (DCDD consent rate at regional PICUs) to 68% (consent rate for donation after brain death in our PICU). Therefore, we assumed a potential range of 40% to 70% as the donation consent rate for NICU DCDD in our calculations. NICU DCDD donors would have provided 16.8 to 39.9 paired

### TABLE 1 Potential Donors After DCDD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WIT 0–59 min ($n=42$)</th>
<th>WIT 60–120 min ($n=15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, d</td>
<td>1–214 (14.5)</td>
<td>2–233 (7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.6–9.9 (3.3)</td>
<td>1.8–7.5 (2.9)</td>
</tr>
<tr>
<td>Gender, no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Urine output, mL/kg/h</td>
<td>1–7.4 (3)</td>
<td>1.5–6.4 (4.3)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.1–1.2 (0.3)</td>
<td>0.2–1.2 (0.5)</td>
</tr>
<tr>
<td>WIT, min</td>
<td>0–57 (27)</td>
<td>60–115 (77)</td>
</tr>
</tbody>
</table>

Unless otherwise noted, data are presented as range (median).

### TABLE 2 Underlying Cause of Death in Potential Donors

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>WIT 0–59 min ($n=42$)</th>
<th>WIT 60–120 min ($n=15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex congenital heart disease</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Neurologic anomaly, or injury</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory failure due to diaphragmatic hernia or lung hypoplasia</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Genetic disorder, multiple congenital anomalies</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Prematurity</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Congenital anomaly: omphalocele, gastroschisis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
kidneys for transplantation in the 10-year study period, or 1.7 to 4 paired kidneys each year, depending on where the NICU consent rate actually falls. Given that no conventional organ donation after brain death occurred in our NICU during this period, en bloc kidney transplantation from newborns could represent a group of donors with a direct impact on the kidney transplantation waiting list.

Although the number of donors may seem small at first glance, the impact of establishing NICU DCDD programs could be significant with nationwide implementation. Based on levels of neonatal care set forth by the Committee on Fetus and Newborn from 2004, level IIIB and level IIIC NICUs should be capable of implementing DCDD programs. Excluding our center, in California alone there are 89 level IIIB and level IIIC NICUs with a total of 2726 NICU beds (1968 level IIIB and 768 level IIIC beds). Assuming a similar number of deaths, elective withdrawals, and donation authorization rates as our unit across this cohort, 55 to 120 paired kidneys could be available annually for transplantation just in California. Extrapolating these data nationally to the 677 level IIIB and IIIC NICUs with 24 043 beds (16 403 level IIIB and 7640 level IIIC beds) in the United States, 487 to 1145 paired donor kidneys could become available each year depending on the acceptance criteria for duration of WIT and actual NICU DCDD consent rates. It should be recognized that although various forms of dialysis can temporarily support patients with ESRD, there is significant associated morbidity and mortality. Kidney transplantation extends life and is also cost-effective in the context of the current era of health care financing. Given that 5000 kidney patients die each year while on the waiting list, any increase in the donor pool by using newborn DCDD donors could potentially be life-saving as well as life-enhancing. This increase could be much more significant than that recently projected and observed in PICUs implementing DCDD programs.

There are several technical limitations that may limit the widespread utilization of newborn donors. These include increased surgical complexity in vascular anastomoses, increased risk of thrombosis, too small of an inferior vena cava, and requirement for additional backbench preparation of the graft. However, at experienced transplant centers, the risks associated with using these small donors may be lowered by focusing on decreasing the ischemic time and improving surgical technique and postoperative management in patients receiving kidneys from such donors.

There are several modalities that permit evaluation and transport of donor kidneys after procurement during the “cold-ischemia time” phase, which may facilitate en bloc transplantation from infant donors. Placing donor kidneys after procurement on a specialized external “pump” permits evaluation of vascular resistance flow, as well as organ viability by evaluating urine production. It also notably improves outcomes by decreasing the prevalence of delayed graft function. Because prolonged cold ischemic time (up to 48 hours) is widely accepted, en bloc kidneys procured from donor newborns can be transported easily to specialized centers willing to transplant these small organs. Thus, implementation of NICU DCDD programs nationwide could feasibly provide donor kidneys for selected transplant centers even if local or regional programs elect not to transplant kidneys from infant donors.

Within our NICU population, withdrawal of life support (discontinuation of ventilator support and/or inotropic support) was the predominant mode of death (45% of the patients died in this manner). This rate is comparable to previous reports of 40% to 64% in US-based studies and 42% to 49% in European studies. Prolongation of the dying process and continued suffering were the major concerns driving the parental decision to stop life-sustaining therapy in our patient population.

At our institution, the administration of comfort care measures is determined by assessment of whether the infant appears comfortable. The parents, nursing staff, and physicians provide this assessment jointly. Surprisingly, there was no documentation of additional comfort medications in 15 of the 57 patients eligible for possible donation. Due to the retrospective nature of our study, we were unable to determine whether these patients were assessed as being comfortable after withdrawal or if medications were given but not accurately documented. In patients undergoing DCDD (as in any patient undergoing withdrawal of life support), the comfort of the patient should be continuously assessed and comfort care provided to ensure that any suffering is avoided.

Because brain death is rare in newborns, it was not unexpected that we did not see this mode of death. In this patient population, brainstem herniation is rare due to the fontanelles being open and the unfused skull sutures that allow for expansion in the case of cerebral edema or intracranial hemorrhage. This situation frequently results in survivors with severe debilitating neurologic injury instead of progression to brain death, which is what occurs with older children. NICU physicians may receive, but have to decline, family requests for organ donation in such terminally ill newborns undergoing withdrawal of life support. However, if DCDD kidney donation programs were implemented in the NICU setting, families would have a new option for donation. Providing this option by expanding newborn DCDD may also have psychological benefits for the
In a recent analysis, further studies autoresuscitation after failed CPR in occurring after withdrawal. However, procurement proceed. There are no procedure. Thus, it will be important to familiarity with OPOs and the donation newborn population, NICU staff lack. Due to the lack of brain deaths in the DCDD.

These physicians cite the possibility of spontaneous resumption of the heart-beat and circulation (autoresuscitation) as a reason for not allowing DCDD. There is no standard DCDD practice for determining the observation time required before declaration of death. The times used range from 2 to 10 minutes based on institutional protocols. The Institute of Medicine recommends observing the patient for 5 minutes after cessation of circulation to preclude autoresuscitation before declaring the patient dead. Only then can organ procurement proceed. There are no reported cases of autoresuscitation occurring after withdrawal. However, autoresuscitation after failed CPR in adult cases has been seen up to 33 minutes after cessation of circulation in a recent analysis. Further studies specific to the newborn population that document the incidence of autoresuscitation may be helpful in addressing these concerns cited by opponents of DCDD.

Due to the lack of brain deaths in the newborn population, NICU staff lack familiarity with OPOs and the donation procedure. Thus, it will be important to educate NICU staff on how to identify and refer potential donors. In addition, a collaborative approach to asking the family about donation, joint management of the potential donor while awaiting a family decision, and leaving invasive monitors in place as life support is withdrawn (to establish the exact time of cessation of circulation) may also require education and changes in NICU practices and protocols.

Depending on the physical distance between the NICU and the operating room, the location of elective withdrawal may need to be discussed by the collaborative team in advance. A well-coordinated process will help to limit WIT if the withdrawal occurs in the NICU and the patient is then transported to the operating room. Our hospital’s DCDD protocol involves withdrawing life support in the operating room whereas routine NICU withdrawals are done in the unit with the NICU staff present. Our hospital’s multidisciplinary organ donation committee has created 2 options for patient families to ensure the least possible disruption. NICU nurses, physicians, and parents may accompany the patient into the operating room for the withdrawal of life support if this is acceptable for the clinical team and family. Alternatively, the recovery room area contiguous to the operating room may be used for the withdrawal process if additional family members wish to be present. Such modifications to policy and procedure should be anticipated, discussed, and individualized at each institution implementing a NICU DCDD program. These modifications will require continued education for staff as well as open communication between the OPO, clinical team, hospital administration, and various hospital committees. PICU colleagues familiar with DCDD protocols and previously involved in DCDD donation can also serve as resources to the NICU physicians.

An additional challenge would be the acceptance of en bloc transplants from neonatal donors by transplant surgeons at other institutions. For the true utilization of this potential donor pool, the number of teams with proficiency in microvascular surgical techniques and willingness to accept smaller donor organs will also need to expand.

Our study is limited by its retrospective design and reflects the experience at a single center. Despite these limitations, our study reports important information on the potential for kidney transplantation from newborn donors. We believe that there needs to be significant education and discussion among NICU staff for implementation of a successful NICU DCDD program. The comfort of the potential donors and the needs of their families also must be addressed for the program to be a success. Identifying clinical predictors of death within 60 or 120 minutes after withdrawal of life support in newborns in future studies may help clinicians determine whether DCDD is even an option before approaching grieving parents for consent.

CONCLUSIONS

During a 10-year period, 42 to 57 newborns and infants undergoing withdrawal of life support in our NICU would have been potential en bloc kidney donors after DCDD. Because brain death is rare in newborns, the use of DCDD would greatly increase the number of potential donors within this population if DCDD programs were implemented in NICUs nationwide.

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